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Stochastic extinction and the selection of the transmission mode in microparasites

Narges Bahi-Jaber[1,2,*], David Fouchet[1] and Dominique Pontier[1]

[1]*Laboratoire de Biométrie et Biologie Evolutive (UMR 5558), CNRS, Université de Lyon, Université Lyon 1, 43 boulevard 11 novembre 1918, 69622 Villeurbanne Cedex, France*
[2]*Laboratoire d' Immunopathologie, Vaccinologie et Biologie Moléculaire, Institut Pasteur de Tunis, 13 Place Pasteur, BP 74, 1002 Tunis, Tunisia*

Stochastic fluctuations in the transmission process of microparasites generate a risk of parasite extinction that cannot be assessed by deterministic models, especially in host populations of small size. While this risk of extinction represents a strong selection pressure for microparasites, it is usually not clearly separated from the deterministic ones. We suggest here that this stochastic selection pressure can affect the selection of the transmission mode of microparasites. To avoid extinction, parasites should maximize their inter-population transmission to ensure frequent reintroductions. Since the types of contacts may differ if congeners belong to the same or distinct populations, strains that are mainly transmitted through inter-population contacts might be selected. To examine this assumption, we analyse the issue of the competition between two strains differing in their transmission mode using a stochastic metapopulation model in which hosts may display different behaviours inside and outside their populations. We show that stochastic selection pressures may drive parasite evolution towards a transmission mode that maximizes the persistence of the parasite. We study the conditions under which stochastic selection pressures may surpass the deterministic ones. Our results are illustrated by the cases of feline immunodeficiency virus in cats and of sexually transmitted diseases in mammals.

Keywords: stochastic selection pressures; R_0; transmission mode; persistence; FIV; STD

1. INTRODUCTION

Why and how do some parasites persist in a host population while others fail to? Why and how does the same parasite successfully invade one population while it rapidly becomes extinct in another population of the same species? Central to almost all theoretical studies on the persistence of infectious diseases is the reproductive number R_0, a threshold defined as the expected number of infections produced by a single infected host in a fully susceptible host population. It is generally admitted that disease extinction (without host population extinction) occurs only if $R_0<1$ (Anderson & May 1986, 1991; Diekmann & Heesterbeek 2000). But R_0 is derived from deterministic models which assume that the host population size is large enough to neglect stochastic fluctuations. This assumption must be relaxed when the total population size or the number of infected hosts is small (e.g. in the early phases of disease invasion; Nasell 2002; Cross *et al.* 2007). In opposition to the classical R_0 argument, stochastic models have revealed that an invasion can fail by chance even if $R_0>1$ (Jacquez & Simon 1993; Diekmann & Heesterbeek 2000). Furthermore, the probability of invasion is positively correlated to R_0 (Lloyd Smith *et al.* 2005) and is strongly dependent on the size and structure of the host population (Keeling & Grenfell 1997; Swinton *et al.* 1998; Read & Keeling 2003).

Any pathogen that cannot easily establish itself in a host population is considered badly adapted to this population and is expected to evolve in order to increase its probability of invasion and/or persistence. It is classically admitted that evolution tends to select parasite strains of the highest R_0 in homogeneous populations under a trade-off between transmissibility and virulence (Ewald 1994; Frank 1996; Messenger *et al.* 1999; Ebert & Bull 2003). Surprisingly, the fact that the risk of stochastic fade-out may represent a strong selection pressure for parasites has been less studied, and it is only very recently that the concept of stochastic selection pressure for parasites has been developed (Andre & Hochberg 2005; Read & Keeling 2007).

In this paper, we argue that the transmission mode of a parasite may be a target trait on which selection can act in order to minimize the probability of extinction. Strong arguments support this hypothesis, such as the existence of a large number of non-sexually transmitted diseases

*Author and address for correspondence: Laboratoire d'Immunopathologie, Vaccinologie et Biologie Moléculaire, Institut Pasteur de Tunis, 13 Place Pasteur, BP 74, 1002 Tunis, Tunisia (narges.bahi@pasteur.rns.tn).

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possessing many of the characteristics of sexually transmitted ones (Lockhart *et al.* 1996), as well as the existence of genetically close pathogens possessing different transmission routes. The most famous example is treponematoses (*Treponema pallidum*), responsible for syphilis, yaws and endemic syphilis (bejel), which are morphologically and antigenically identical (Noordhoek *et al.* 1990) but differ in their transmission mode (Antal *et al.* 2002). Thrall & Antonovics (1998) have addressed the selection of the transmission mode for parasites that have both sexual and non-sexual transmission routes in relation to the number of sexual and non-sexual contacts. Using a deterministic approach, they showed that the evolutionary outcome depends on whether or not the transmission mode is accompanied by an impact of the disease on host survival and fecundity. However, they do not consider stochastic fluctuation effects as well as the social and spatial structuring of host populations, which underlies the contact network of the host population.

To precisely assess the role of stochastic fade-out as a selection pressure on the transmission mode of micro-parasites, one has to examine both the inter- and intra-population contacts. Indeed, in a metapopulation, individuals may display different behaviours inside and outside their social group. This is well documented in animal populations where certain kinds of behaviours are more frequently expected at the intra-group level (e.g. 'social' behaviours like sharing food or grooming), while others are more frequently observed among individuals coming from distinct subpopulations (e.g. aggressive behaviours; see Liberg *et al.* (2000) in cats *Felis catus*, Farabollini *et al.* (1991) in rabbits *Oryctolagus cuniculus*, see also Lazaro-Perea (2001)). Consequently, the transmission rate of a parasite can be split into two terms: an intra-population transmission rate and an inter-population transmission rate. The balance between those two terms is expected to vary depending on the transmission mode of the parasite, and thus on the nature of the at-risk contacts. A given transmission mode may be supported by a kind of at-risk contact that is more frequent between individuals coming from the same population, leading to an intra-population rate higher than the inter-population one. Another transmission mode may be related to inter-population at-risk contacts and the inter-population transmission rate will be higher than the intra-population one. The transmission mode of a parasite strain in a host population with a given spatial and social structure is thus a key factor in the persistence of the strain and in its probability of stochastic fade-out. Consequently, the fitness of a strain is likely to depend on its mode of transmission and on the structure of the host population. Our basic hypothesis is that, according to the structure of the host population, evolution may select for the transmission mode with inter- and intra-transmission rates that maximize the persistence of the parasite.

2. METHOD

2.1. The model

We develop a stochastic metapopulation model in which hosts may display different behaviours inside and outside their population, and we analyse the competition of two strains differing in their transmission mode. The model is based on the fundamental assumption that the behaviour of a host facing a congener may be different depending on whether or not the congener comes from the same population. The metapopulation is composed of a set of n connected local populations of small size. In our approach, connection occurs through inter-population contacts between individuals that do not migrate from their population. Our model differs in this regard from migration-based metapopulation models. We assume a logistic growth in each population with the same carrying capacity Ω. To prevent permanent host population extinction (especially in the case of small host population size), we add a constant reintroduction rate c, identical for all populations.

We consider a disease without recovery, and we assume no co-infection between strains that compete for the same limited resource: the susceptible part of the host population. Evolutionary dynamics can be easily derived from the study of strains' competition if we assume that mutations are rare enough to ensure that only two strains are present simultaneously in a host metapopulation. We consider the competition of two strains, a and b, that differ in their transmission mode. We assume that the difference in the transmission mode results in different intra- and inter-population transmission rates, which model the difference in the frequency of associated intra- and inter-population at-risk contacts. Let x represent strain a or b and denote β^x_{intra} and β^x_{inter} the intra- and inter-population transmission rates, respectively, in the ith population. We suppose that the frequency of each type of contact may be a function of the host density, so that $\beta^x_{i,\mathrm{intra}} = \tilde{\beta}^x_{\mathrm{intra}} N_i^k$ and

$$\beta^x_{i,\mathrm{inter}} = \tilde{\beta}^x_{\mathrm{inter}} \sum_{j \neq i} N_j^k,$$

where N_i is the size of the ith host population of the metapopulation ($i \in \{1, \ldots, n\}$) and $k \in \mathrm{IR}$. The case of $k=0$ corresponds to the so-called frequency-dependent transmission, while if $k=1$ we have a density-dependent transmission. Moreover, we consider the regular reintroduction of each strain by the contact between a susceptible host of the metapopulation and an infected host outside the metapopulation at a rate ε.

Let S_i be the number of susceptible hosts, I_i^{a} and I_i^{b} be the number of hosts infected by strains a and b, respectively, in the ith population ($i \in \{1, \ldots, n\}$). We denote the host birth rate by σ and the natural death rate by m. Finally, we denote the virulence by α_x $x \in \{\mathrm{a},\mathrm{b}\}$, that is, the additional mortality rate induced by the strain. A flow diagram of the compartmental model is given in figure 1.

Since we focus on the risk of extinction as a selection pressure for the parasite transmission mode, we must account for the effect of demographic stochasticity. The model is event driven and is based on a continuous-time Markov process. Events and their associated probabilities in one population are given in table 1. The deterministic behaviour of the system is described by a set of differential equations given in appendix A.

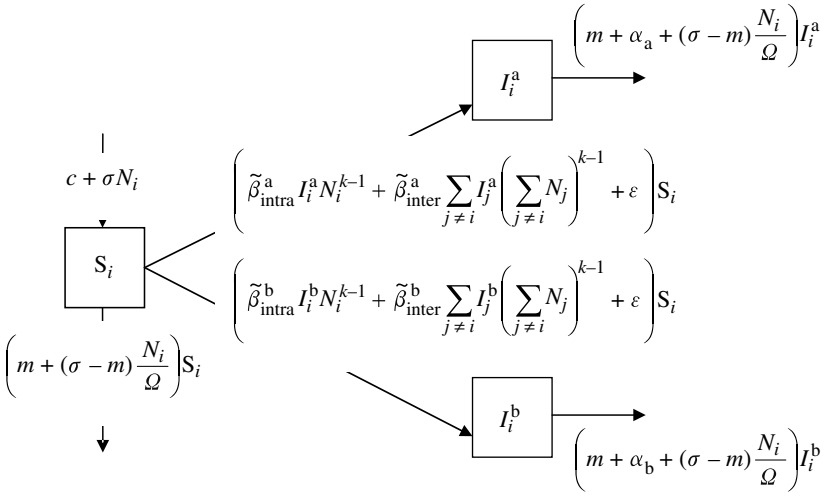

Figure 1. Flow diagram between the classes of the model for the ith population of the metapopulation: susceptible (S_i), infected with strain a (I_i^{a}) and infected with strain b (I_i^{b}).

Table 1. Transition rates of the Markovian model.

event	change in state	probability of the event
birth of a susceptible	$(S_i, I_i^{\mathrm{a}}, I_i^{\mathrm{b}}) \to (S_i+1, I_i^{\mathrm{a}}, I_i^{\mathrm{b}})$	$\tau_{i,1} = c+\sigma N_i$
death of a susceptible	$(S_i, I_i^{\mathrm{a}}, I_i^{\mathrm{b}}) \to (S_i-1, I_i^{\mathrm{a}}, I_i^{\mathrm{b}})$	$\tau_{i,2} = (m+(\sigma-m)(N_i/\Omega))S_i$
death of an infected I_{a}	$(S_i, I_i^{\mathrm{a}}, I_i^{\mathrm{b}}) \to (S_i, I_i^{\mathrm{a}}-1, I_i^{\mathrm{b}})$	$\tau_{i,3} = (m+\alpha_{\mathrm{a}}+(\sigma-m)(N_i/\Omega))I_i^{\mathrm{a}}$
death of an infected I_{b}	$(S_i, I_i^{\mathrm{a}}, I_i^{\mathrm{b}}) \to (S_i, I_i^{\mathrm{a}}, I_i^{\mathrm{b}}-1)$	$\tau_{i,4} = (m+\alpha_{\mathrm{b}}+(\sigma-m)(N_i/\Omega))I_i^{\mathrm{b}}$
infection by strain a	$(S_i, I_i^{\mathrm{a}}, I_i^{\mathrm{b}}) \to (S_i-1, I_i^{\mathrm{a}}+1, I_i^{\mathrm{b}})$	$\tau_{i,5} = \left(\tilde{\beta}^{\mathrm{a}}_{\mathrm{intra}} I_i^{\mathrm{a}} N_i^{k-1}+\tilde{\beta}^{\mathrm{a}}_{\mathrm{inter}}\sum_{j\neq i} I_j^{\mathrm{a}}\left(\sum_{j\neq i} N_j\right)^{k-1}+\varepsilon\right)S_i$
infection by strain b	$(S_i, I_i^{\mathrm{a}}, I_i^{\mathrm{b}}) \to (S_i-1, I_i^{\mathrm{a}}, I_i^{\mathrm{b}}+1)$	$\tau_{i,6} = \left(\tilde{\beta}^{\mathrm{b}}_{\mathrm{intra}} I_i^{\mathrm{b}} N_i^{k-1}+\tilde{\beta}^{\mathrm{b}}_{\mathrm{inter}}\sum_{j\neq i} I_j^{\mathrm{b}}\left(\sum_{j\neq i} N_j\right)^{k-1}+\varepsilon\right)S_i$

2.2. Parameter estimation and simulations

To determine the issue of the competition between the two strains characterized by different transmission modes (i.e. to determine which transmission mode is selected) in the metapopulation over 200 units of time period, simulations of the stochastic model are performed using Gillespie's direct algorithm. This algorithm considers the time between two distinct events as a random continuous variable (see electronic supplementary material, appendix S1, for details). We perform 1000 simulations of the stochastic model, using the same parameter values and starting with identical initial conditions for all simulations. From this set of non-identical realizations of the model, we estimate the proportion of simulations for which we have at each time either the coexistence of both strains, or only strain a, or only strain b, or the extinction of both strains. Each simulation starts with one individual infected by strain a in one population and one individual infected by strain b in another population.

Since the model is purely theoretical and is not based on any biological system, we choose a set of arbitrary standard values for parameters and we proceed to a sensitivity analysis of the prediction of the model to parameter values (see §3 for more details). All parameters of the model are summarized in table 2, and their standard values as well as other tested values are given if they exist.

3. RESULTS

The reproductive number of one strain can be written as $R_0^x = R^x_{0,\mathrm{intra}} + R^x_{0,\mathrm{inter}}$ where $R^x_{0,\mathrm{intra}} = (\Omega^k \tilde{\beta}^x_{\mathrm{intra}})/(\sigma+\alpha_x)$ and $R^x_{0,\mathrm{inter}} = (((n-1)\Omega)^k \tilde{\beta}^x_{\mathrm{inter}})/(\sigma+\alpha_x)$. The deterministic version of the model predicts that the strain with the highest R_0 invades the parasitic population, provided that $R_0 > 1$ and infects all the host metapopulation as soon as its β_{inter} is not null (see figure 2*a*). This prediction is in agreement with previous studies which have revealed that the parasite strain with the largest R_0 is evolutionarily stable (Day & Proulx 2004), particularly in the absence of co- or super-infection (Nowak & May 1994; May & Nowak 1995). The results derived from the stochastic version with the same set of parameters show a broad spectrum of outcomes, which contrast with the all-or-nothing predictions of the deterministic model. Contrary to deterministic predictions, strain b, which has lower R_0 but higher inter-population transmission rate than strain a, has a higher probability of persistence (figure 2*b*). This suggests the existence of stochastic selection pressures that give an advantage to the strain b against deterministic selection pressures.

We analyse now how the strength of the advantage of the strain with a higher inter-population transmission rate depends on the value of the parameters of the host–parasite system. To this aim, we fix the values of the

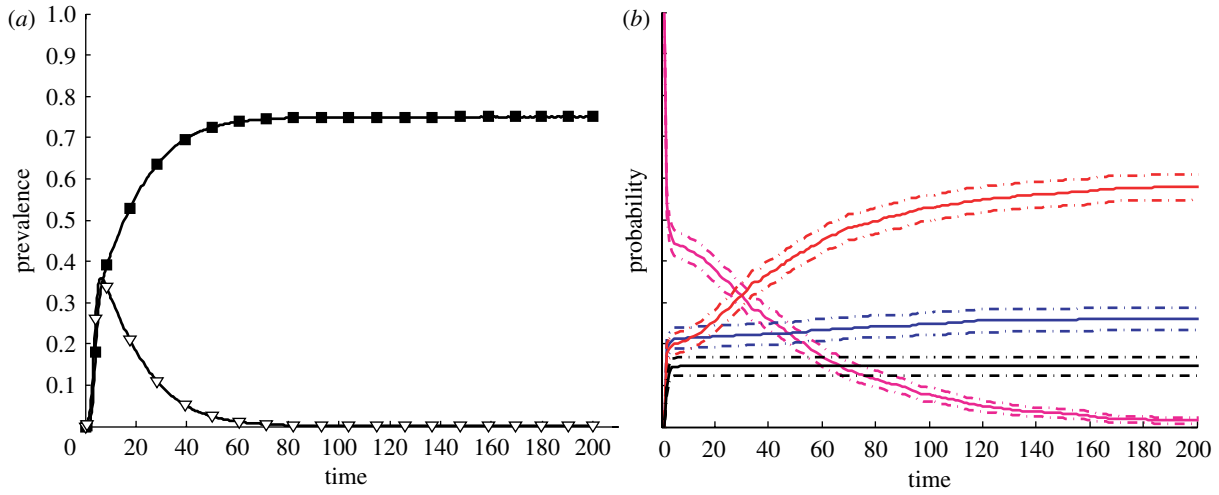

Figure 2. Comparison between deterministic and stochastic outcomes of the model for the same set of parameters $\tilde{\beta}^{a}_{inter}=0.1$, $\tilde{\beta}^{a}_{intra}=2$, $\tilde{\beta}^{b}_{inter}=1$, $\tilde{\beta}^{b}_{intra}=0.8$, $\sigma=0.5$, $m=0.1$, $\alpha_a=\alpha_b=0.1$, $K=20$ and $k=0$ leading to $R^a_0=3.5$, $R^b_0=3$. (*a*) Prevalence of strain a (squares) and strain b (triangles) in the metapopulation predicted by the deterministic model. (*b*) Probability of finding in the metapopulation both strains (magenta), only strain a (blue), only strain b (red) or none of both strains (black) bounded by 95% CIs.

Table 2. Standard values of the parameters and alternative values tested.

		value	
parameter	symbol	standard	tested (if any)
intrinsic parameters			
birth rate	σ	0.5	
natural death rate	m		
carrying capacity of a population	Ω	10	5, 20, 50, 100
host reintroduction rate	c	10^{-1}	
form of the incidence function	k	0	-1, -0.5, 0.5, 1, 1.5, 2
intra-population transmission rate of strain a	$\beta^{a}_{i,intra}=\tilde{\beta}^{a}_{intra}N_i^k$		
intra-population transmission rate of strain b	$\beta^{b}_{i,intra}=\tilde{\beta}^{b}_{intra}N_i^k$		
inter-population transmission rate of strain a	$\beta^{a}_{i,inter}=\tilde{\beta}^{a}_{inter}\sum_{j\neq i}N_j^k$		
inter-population transmission rate of strain b	$\beta^{b}_{i,inter}=\tilde{\beta}^{b}_{inter}\sum_{j\neq i}N_j^k$		
external transmission rate	ε	0.005	
mortality rate due to infection by strain a	α_a	0.1	
mortality rate due to infection by strain b	α_b	0.1	
other parameters			
reproductive rate of strain a	R^a_0	3.5	
reproductive rate of strain b	R^b_0	3.5	2.45, 2.8, 3, 3.15
ratio of reproductive rates	$\rho=R^b_0/R^a_0$	1	0.7, 0.8, 0.9
ratio of inter-population transmission rates	$\omega=\tilde{\beta}^{b}_{inter}/\tilde{\beta}^{a}_{inter}$	10	1, 2, 5, 20

reproductive number (R^a_0) and the inter-population transmission rate ($\tilde{\beta}^{a}_{inter}$) of the strain a. This fixes the value of the intra-population transmission rate $\tilde{\beta}^{a}_{intra}=((R^a_0(\sigma+\alpha))/\Omega^k)-\tilde{\beta}^{a}_{inter}(N-1)^k$. To analyse the competition between the two strains differing in their mode of transmission, we fix the value of the reproductive number of the strain b by setting $R^b_0=\rho R^a_0$ and we vary the relative role played by inter- and intra-population transmission rates in the transmission of the strain b by setting $\tilde{\beta}^{b}_{inter}=\omega\tilde{\beta}^{a}_{inter}$ and thus $\tilde{\beta}^{b}_{intra}=((\rho R^a_0(\sigma+\alpha))/\Omega^k)-\omega\tilde{\beta}^{a}_{inter}(N-1)^k$. In this way, on one hand, the values of the reproductive numbers of the two strains are constant whatever the relative values of inter- and intra-population transmission rates, and they determine the deterministic prediction of the model. On the other hand, the two strains differ in their transmission mode since they differ in their relative values of inter- and intra-population transmission rates, and we can thus analyse the impact of the transmission mode on the persistence of both strains according to the structure of the host population.

To eliminate deterministic components of selection pressures acting on the parasite, we take the same reproductive number for the two strains to focus only on stochastic effects. The ratio of the inter-population transmission rates of the two strains (ω) plays a

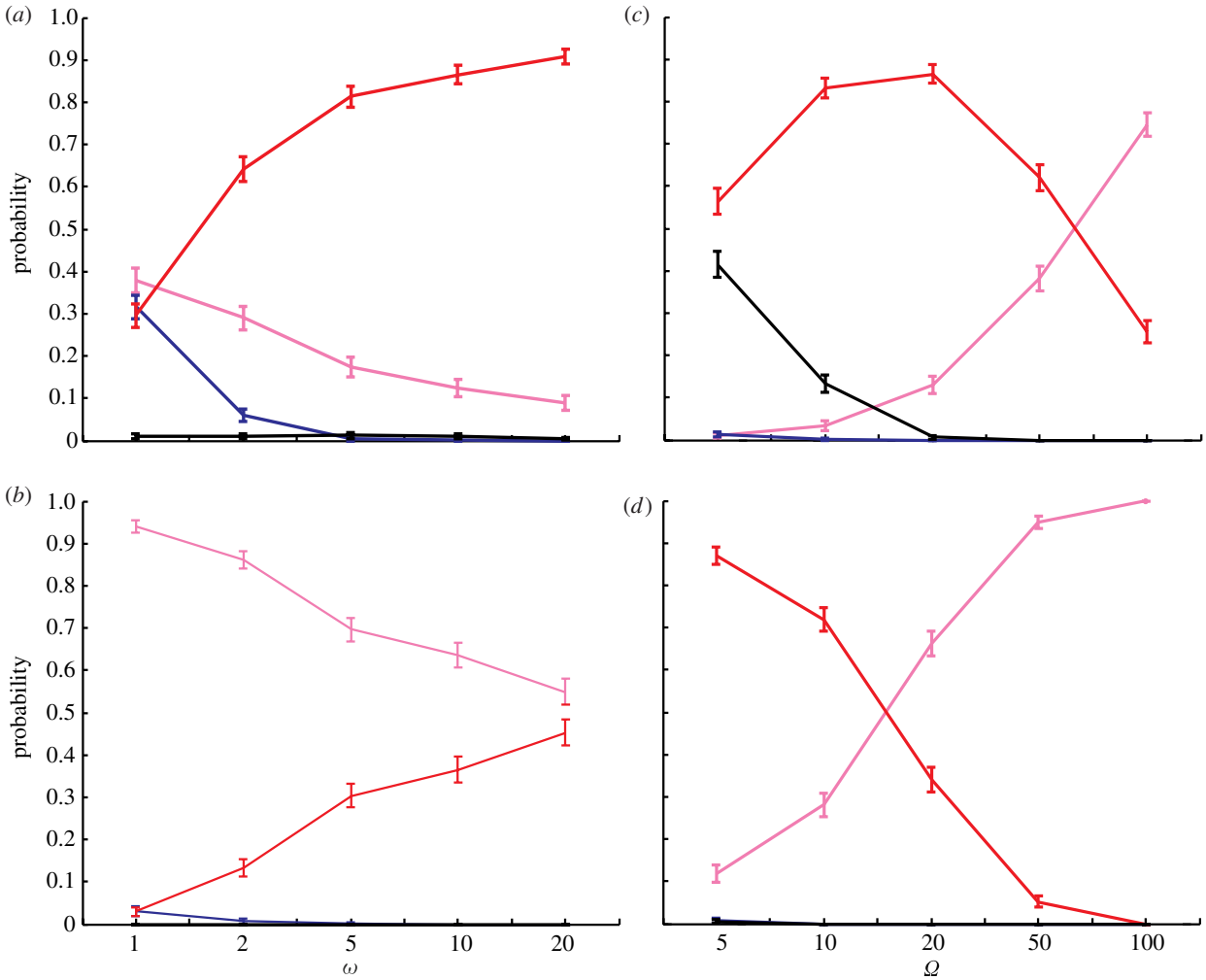

Figure 3. Sensitivity of stochastic model predictions on parameter values in the absence of deterministic selection pressures (i.e. $R_0^{\mathrm{a}} = R_0^{\mathrm{b}} = 3.5$). Influence of the ratio of inter-population transmission rates ($\omega = \tilde{\beta}_{\mathrm{inter}}^{\mathrm{b}}/\tilde{\beta}_{\mathrm{inter}}^{\mathrm{a}}$) at (*a*) the population level and (*b*) the metapopulation level. Influence of the host population size (Ω) at (*c*) the population level and (*d*) the metapopulation level. Probability to find both strains (magenta), only strain a (blue), only strain b (red) or none of both strains (black) bounded by 95% CIs.

fundamental role in the issue of the competition. When $\omega = 1$ (i.e. when the two strains are identical in terms of R_0 and of the values of inter- and intra-population transmission rates) we find the same probability that one population will be infected by either only strain a, or only strain b, or by both strains (figure 3*a*). At the metapopulation level (figure 3*b*), the probability that only one strain invades the metapopulation is very low and identical for both strains, while there is a very high probability that the two strains co-circulate in the metapopulation. As soon as ω increases (i.e. when strain b has a higher inter-population transmission rate than strain a), the probability of finding only strain b in a population increases while the probability of finding only strain a decreases. For high values of ω, the probability that one population of the metapopulation is infected only by strain a is null and, despite its reintroduction from outside the metapopulation, there is only a very low probability of finding a population co-infected by the two strains (figure 3*a*). At the metapopulation level, even if the probability of coexistence is high due to external reintroduction, the more the transmission is made through inter-population contacts, the higher is the probability that strain b invades the whole metapopulation (figure 3*b*). The strain a with a lower rate of inter-population transmission is likely to suffer frequent local extinctions that cannot be balanced by reintroductions before the invasion of the population by strain b. Consequently, this strain may be at an evolutionary disadvantage when competing with a more diffusing strain, even if they have the same R_0.

The evolutionary advantage of the strain with the highest inter-population transmission rate also depends upon the size of the populations in its host metapopulation. While deterministic outcomes are independent of the size of the population, stochastic results show that the smaller the population size, the more the strain with a high inter-population transmission rate is favoured (figure 3*c*,*d*). When the population size is small, the probability of parasite extinction is high. In a metapopulation of small size populations, both the strains suffer frequent local extinctions. But the strain with the higher rate of inter-population transmission is more likely to be

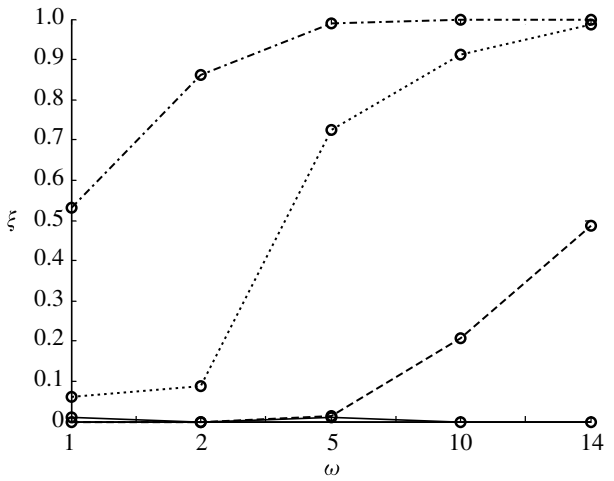

Figure 4. Strength of the stochastic selection pressures (ξ=(Proba (only strain b in a population))/(Proba (only strain a in a population))+(Proba (only strain b in a population))) according to the ratio between the inter-population transmission rate of the two strains (ω) for different values or $\rho = R_0^b/R_0^a$. Values of $\xi < 50\%$ mean that a is advantaged, values of $\xi > 50\%$ mean that b is advantaged. Solid line, $\rho = 0.7$; dashed line, $\rho = 0.8$; dotted line, $\rho = 0.9$; dot–dash line, $\rho = 1$.

reintroduced into an uninfected population and to invade it than the other strain. Step by step, it can infect all of the populations, leading to the extinction of the strain with the lower inter-population transmission rate at the metapopulation level. In a metapopulation of large populations, stochastic selection pressures are very low. As the two strains have the same R_0, neither is advantaged and the two strains circulate identically; thus the two transmission modes coexist within the metapopulation.

Finally, we can note that the issue of the competition between the two strains does not depend upon the form of the incidence function (see electronic supplementary material, appendix S2, for more details).

We now wish to estimate the relative strength of stochastic pressures to deterministic ones. We define the advantage of the strain b(ξ) as the probability of finding only strain b in one population of the metapopulation divided by the probability of finding only strain a plus the probability of finding only strain b in the same population. A value higher than 50% indicates that strain b is advantaged, while a value lower than 50% indicates that strain a is advantaged. We then evaluate how ξ varies according to decreasing values of ρ (the ratio between the R_0 of strain b and the R_0 of strain a) and increasing values of ω (the ratio between the inter-population transmission rate of strain b and that of strain a; figure 4). In this way, we can evaluate how much higher the inter-population transmission rate of strain b must be than the inter-population transmission rate of strain a to compensate for a lower R_0.

For ρ near to 1 (i.e. for two strains with close R_0), a slightly higher inter-population transmission rate gives to strain b a strong advantage that makes strain a unable to invade a host population. But if the difference between the R_0 of the two strains is high, even a very high level of inter-population transmission rate of the strain b is not sufficient for this strain to invade a host population. The lower the reproductive number of strain b is, the higher must its inter-population transmission rate be to give it an evolutionary advantage. If the difference between the two R_0 values is too high, deterministic selection pressures that give advantage to strain a are stronger than stochastic ones that favour strain b.

4. DISCUSSION

Many studies have demonstrated the stochastic effect of local versus global transmission on the dynamics of an infectious disease (Ball & Neal 2002; Koopman *et al.* 2002; Cross *et al.* 2005). From an evolutionary point of view, while many stochastic models have shown how the host population structure may drive the evolution of some traits of the host–parasite interaction (e.g. Haraguchi & Sasaki (2000) and Boots *et al.* (2004) for the evolution of the virulence; Keeling (2000) and Read & Keeling (2003) for the evolution of the transmission rate), very few have separated stochastic from deterministic selection pressures (but see Andre & Hochberg 2005; Read & Keeling 2007). Here, we show that taking the stochastic selection pressures due to the risk of stochastic fade-out into account reveals a mechanism through which the transmission mode of a microparasite can be selected according to the structure of the host population. The selection of the transmission mode appears to be due to stochastic selection pressures that, under certain conditions, may overcome the deterministic ones.

Deterministic pressures tend to select for strains with the highest reproductive number and stochastic ones those with the highest inter-population transmission rate. Depending on the characteristics of the host population, it is either deterministic or stochastic pressures that dominate and drive the selection of the transmission mode. The competition between the two strains differing in their transmission mode may lead to either the invasion of the host population by one of the two strains, leading to the infection of the population by a parasite with a unique transmission mode, or the coexistence of the two strains with different transmission modes. It is interesting to note that it is effectively the competition between the strains (i.e. the fact that a host infected by a strain is protected against the other) that generates this mechanism. The performance (in terms of probability of extinction and mean prevalence) of one strain independently does not depend on the fraction of transmission made between populations (see electronic supplementary material, appendix S3).

4.1. The impact of population size

Among the parameters that determine the strength of stochastic section pressures, the size of the host population appears to be the most important. In deterministic models, parasite fitness is estimated by a deterministic mathematical expression, based most often on the R_0 of the parasite. The evolutionary outcome of the competition between different strains of the parasite is thus dependent only on the fitness of

each strain, and is sensitive only to the parameters involved in the R_0 expression of each strain. In particular, the size of the host population, even if it determines the value of the R_0 in a density-dependent transmission case, for example, does not modify the ratio between the R_0 of two competing strains and thus does not modify the deterministic selection pressures.

In contrast, when the fitness of the parasite is estimated by taking into account the risk of stochastic fade-outs, the size of the host population plays a crucial role in the evolutionary dynamics of the disease. Decreasing the size of the population increases the risk of stochastic extinction and thus largely alters the advantage of a strain that does not quickly spread among populations. In these conditions, the competition is driven not only by the values of the R_0 but also by the ability of the strains to be transmitted among populations (parameter ω in our model) and thus to be frequently reintroduced into the host population.

In our model, we have considered that all the populations have a density-dependent growth with the same carrying capacity. Results would differ with a source-sink pattern. The introduction of one or more large populations in the metapopulation is likely to enhance the persistence of a strain with a low inter-population transmission rate and thus is likely to change the issue of the competition between the strains. It will be interesting to investigate more deeply this point.

4.2. The relative importance of intra- and inter-population transmission mode

In the deterministic model, only the sum of the intra- and inter-population reproductive numbers of a strain is considered. Their relative values do not affect the outcomes of the model. In contrast, the evolutionary dynamics predicted by the stochastic model is highly sensitive to the ratio between the inter- and intra-population reproductive numbers of a strain. In particular, if the host population is structured into small populations, the inter-population R_0 is likely to play a fundamental role in the evolution of the microparasite.

In most metapopulation models, the inter-population transmission rate is assumed to be proportional to the intra-population one (Rohani *et al.* 1999), and, thus, increasing the coupling between populations implies an increase in the global transmission rate. This means that the same types of contacts are involved at both the intra- and the inter-population levels. However, this parsimonious assumption may not hold in real populations because individuals may display different behaviours inside or outside their social group or population. Consequently, a parasite may evolve to maximize its inter-population transmission, by selecting a transmission mode which is related to the behaviours displayed by individuals during inter-population contacts, at the expense of the intra-population transmission. As a result, according to the contact structure and the size of the host metapopulation, either the local or the global transmission could be favoured to maximize microparasite transmission.

4.3. The case of feline immunodeficiency virus and sexually transmitted diseases

Despite the small number of studies addressing the question of the selection of the transmission mode, the epidemiological pattern of some viruses may be understood in light of our results. For example, under natural conditions, the feline immunodeficiency virus (FIV; Pedersen 1992) is transmitted through bites during fights between males, or mating between males and females (Bendinelli *et al.* 1995; Pontier *et al.* 1998). However, several different transmission modes (e.g. sexual or vertical) of specific strains have been reported experimentally (O'Neil *et al.* 1995; Jordan *et al.* 1998). The analysis of the spatial and social structure of cat populations can explain the selective advantage of the transmission by bites compared with other existing routes. Indeed, cats live in small polygynous groups in which contacts between congeners from different groups are almost exclusively restricted to fights between males, leading to frequent bites, or mating, during which the male often bites the female at the neck (Courchamp *et al.* 1998, 2000; Liberg *et al.* 2000). The dominant males can roam over long distances in search of receptive females and get involved in fights. These contacts may provide opportunities for the FIV to spread between and to be reintroduced into cat populations. In this context, the strains of FIV that are transmitted through bites should have the highest probability of infecting a cat population. This may explain the apparent paradox of FIV, which exhibits an endemic pattern despite its low prevalence restricted to adult males (Courchamp *et al.* 1998, 2000).

The host range of sexually transmitted viruses can be interpreted in the same manner. It is commonly admitted that sexual transmission is expected to be favoured in low-density populations, whereas non-sexual transmission would be more likely found in high-density populations (Smith & Dobson 1992; Thrall & Antonovics 1998). Furthermore, sexually transmitted diseases are predominantly found in large mammals living in small social groups such as primates or artiodactyls (Lockhart *et al.* 1996). In these species, the rare occasions that congeners from distinct groups come into contact are principally related to mating. In such conditions, our results predict that a sexually transmitted strain may persist better in such populations than a non-sexually transmitted one.

To conclude, the transmission mode of a parasite, like its transmission rate or virulence, should be regarded as a potential target of natural selection. This should be considered carefully since animal populations are more and more subject to modifications of their environment, and, as a result, of their contact structure. Actually, habitat loss of natural populations resulting in population fragmentation or, in contrast, aggregation and increase of local densities, provide mechanisms likely to modify the relative weight of inter- and intra-population transmission rates in the persistence of a microparasite and, in turn, the selection pressures on its transmission mode.

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APPENDIX A

The deterministic model corresponding to the continuous-time Markov process described in §2 is as follows:

$$\frac{\mathrm{d}S_i}{\mathrm{d}t} = \sigma N_i - \left(m + (\sigma - m)\frac{N_i}{\Omega}\right) S_i - \left(\tilde{\beta}^{\mathrm{a}}_{\mathrm{intra}} I^{\mathrm{a}}_i N_i^{k-1} + \tilde{\beta}^{\mathrm{a}}_{\mathrm{inter}} \sum_{j\neq i} I^{\mathrm{a}}_j \left(\sum_{j\neq i} N_j\right)^{k-1} + \tilde{\beta}^{\mathrm{b}}_{\mathrm{intra}} I^{\mathrm{b}}_i N_i^{k-1} + \tilde{\beta}^{\mathrm{b}}_{\mathrm{inter}} \sum_{j\neq i} I^{\mathrm{b}}_j \left(\sum_{j\neq i} N_j\right)^{k-1}\right) S_i,$$

$$\frac{\mathrm{d}I^{\mathrm{a}}_i}{\mathrm{d}t} = -\left(m + \alpha_{\mathrm{a}} + (\sigma - m)\frac{N_i}{\Omega}\right) I^{\mathrm{a}}_i + \left(\tilde{\beta}^{\mathrm{a}}_{\mathrm{intra}} I^{\mathrm{a}}_i N_i^{k-1} + \tilde{\beta}^{\mathrm{a}}_{\mathrm{inter}} \sum_{j\neq i} I^{\mathrm{a}}_j \left(\sum_{j\neq i} N_j\right)^{k-1}\right) S_i,$$

$$\frac{\mathrm{d}I^{\mathrm{b}}_i}{\mathrm{d}t} = -\left(m + \alpha_{\mathrm{b}} + (\sigma - m)\frac{N_i}{\Omega}\right) I^{\mathrm{b}}_i + \left(\tilde{\beta}^{\mathrm{b}}_{\mathrm{intra}} I^{\mathrm{b}}_i N_i^{k-1} + \tilde{\beta}^{\mathrm{b}}_{\mathrm{inter}} \sum_{j\neq i} I^{\mathrm{b}}_j \left(\sum_{j\neq i} N_j\right)^{k-1}\right) S_i.$$

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